Swedish Science Pioneers

Journal of Experimental & Clinical NeuroSciences

Journal homepage : www.JECNS.com

Review Article

Novel Quantitative Approach in Functional and Structural Imaging of Brain in Normal Ageing and Neurodegenerative Disorders: Part II. Clinical Applications of Positron Emission Tomography

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Received: 2018-09-10

Accepted: 2018-12-02

DOI:10.13183/jecns.v6i1.95

Abstract

Aging results in measureable alterations in brain anatomy and function. Several theories about the origins of brain aging have been developed. Inflammation, replicative senescence, continuous shortening of chromosomes (telomere theory), and oxidative stress, are amongst factors affecting life span. Also, Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common age-related neurodegenerative disorders. As a highly prevalent health problems, the accurate identification of these disorders is challenging. Modern functional and structural imaging such as positron emission tomography (PET) and magnetic resonance imaging (MRI) might allow investigators to better understand pathophysiologic changes in AD and PD. However, these technics have several flaws which limit their use in clinical settings. Here, we deep dive into the existing and novel quantitative approaches of PET imaging for normal aging and its applications in neurodegenerative disorders such as AD and PD.

Keywords: *Functional Neuroimaging, Brain, Neurodegenerative Disorders, Positron Emission Tomography, Magnetic Resonance Imaging*

Normal Aging Brain

Normal aging is associated with a progressive decline in cognitive performance, including perception, attention, language and memory [1-3]. Age-related functional and biochemical changes in the brain include alterations in cerebral metabolism, cerebral blood flow and neurotransmitter function. With the advent of functional neuroimaging techniques, these biochemical changes can be measured in vivo throughout the life span of person. Because functional disturbances herald structural changes, imaging with positron emission tomography (PET) may yield abnormal results whereas the brain anatomy appears to be normal. Several positron-labeled tracers have been presented to discern the distribution and activity of age-related biochemical changes in the brain.

Change of Cerebral Metabolism

There is an inconsistency in 18-fluorodeoxyglucose (FDG)-PET findings for aging brain. A number of studies in normal aging subjects have shown significant decrease in whole brain glucose metabolism with advancing age, while others have noted no noticeable change. Although some decline in local glucose metabolism in the temporal, parietal, and frontal areas has been reported by some studies, others have revealed that the prefrontal cortex is the most important region affected by aging. The divergence in results may be due to different methodologies, screening criteria, range of subject ages, and especially sample size, which is one of the key factors for obtaining consistent statistical results. In addition, most early studies on age-related glucose metabolism used region of interest (ROI) analysis. However, recently voxel-based analysis such as Statistical Parametric Mapping (SPM) package, have been widely used to help detect the area missed in ROI analysis and avoid subjective variation.

Several studies have now characterized the effect of aging on the distribution of glucose metabolism using FDG-PET.

Kuhl et al. [4] reported the use of FDG-PET for determining patterns of local cerebral glucose utilization in 40 normal

volunteer subjects aged between 18-78 years. They found a gradual decline in mean cerebral metabolic rates of glucose (CMRglc) with age. The mean CMRglc was found to be, around 26% less at age 78 compared with 18 years. Superior and posterior inferior frontal regions displayed the most swift decrease with age.

Alavi et al. [5] evaluated 23 healthy aged individuals with a mean age of 65±10 years and 21 young controls with a mean age of 27±6 years using FDG-PET. A general drop in CMRglc in the frontal and somatosensory regions was revealed in the respected study.

Yoshii et al. [6] investigated 76 normal volunteers aged 21-84 years with FDG-PET. In this study, when brain atrophy was excluded, mean CMRglc had lower values in elderly than in young individuals, with statistically substantial differences in the frontal, parietal and temporal areas. Likewise, women had meaningfully greater mean CMRglc than that of men. When covariate analysis was applied to include brain atrophy, because brain volume was greatly associated with age, the impacts of age and sex on CMRglc were no longer noteworthy.

Loessner et al. [7] conducted FDG-PET in 120 healthy volunteers aged between 19-79 years. The most consistent outcome linked to healthy aging was a decrease in cortical glucose metabolism, chiefly in the frontal lobes. A slight decline in frontal glucose metabolism was revealed in the third and fourth decades of life, but a more intense drop was realized after the sixth decade of life. Temporal, parietal and occipital lobe glucose metabolism exhibited substantial discrepancy both within and across age groups. Other regions, including basal ganglia, hippocampus, thalami, cerebellum, posterior cingulate gyri and visual cortex to be metabolically unaffected.

Willis et al. [8] assessed CMRglc in 66 healthy adults, aged between 20-69 years using SPM95. Significant age-related decrease in global CMRglc was noted in the entire sample as along with widespread and bilateral decrease in cortical regional CMRglc. However, significant positive correlations of age with normalized regional CMRglc were observed in the cerebellum, thalamus and occipital areas.

Kalpouzos et al. [9] used FDG-PET and voxel-based methodologies such as voxel-based morphometry (VBM) for partial volume correction (PVC) in 4 healthy subjects aged between 20-83 years and correlated between age and both grey matter (GM) volume and FDG uptake. They observed that the frontal cortex manifested the greatest deterioration, both structurally and functionally, whereas the anterior hippocampus, thalamus and the posterior cingulate cortex were the least affected.

Pardo et al. [10] studied FDG-PET findings in 46 healthy subject age between 18-90 years. The authors found focal decrease in brain activity, with the largest declines localized in the medial network comprising the prefrontal cortex, anterior cingulate cortex, dorsomedial thalamus and basal forebrain. Moreover, decline in metabolism in this network correlated with decline in cognitive function.

Hsieh et al. [11] examined FDG-PET in 100 healthy subjects using SPM99 for analysis. Decreased brain metabolism with aging was found bilaterally in the lateral orbital prefrontal and right anterior cingulate cortices.

Shen et al. [12] tested the effect of age on CMRglc using FDG-PET analyzed by SPM5 in 108 females (aged between 26-71 years) and 126 males (aged between 28-77 years) who had a normal physical examination. Brain activity in the frontal lobe and superior temporal gyri declined with normal aging in both gender groups. Another finding was the metabolic decline with normal aging in the left cerebrum, which showed greater significance and larger range compared with the right cerebrum.

Although there are some inconsistencies, the most similar finding is that the frontal cortex shows the greatest effect of decreased cerebral glucose metabolism. The most frequently reported regions are the prefrontal cortex, inferior frontal cortex and anterior cingulate cortex. This major involvement in frontal lobe may agree with neurological findings of normal aging subjects in physical examination, such as executive deficits and declined cognitive function such as working memory, task switching and inhibitory control.

Alongside alterations in GM, healthy aging is also characterized by fluctuations within the white matter (WM) [13]. Along with WM hyperintensities, structural and functional connectivity variations and changes of WM tract integrity have been consistently described. Histopathological studies have revealed age-related damage of myelinated fibers in the WM. Chetelat et al. [13] assessed whether CMRglc fluctuations in healthy aging was linked to age-related changes of the structural integrity and/or functional connectivity of the WM. FDG-PET data from 40 young and 57 elderly healthy volunteers were examined with the WM volume from T1-weighted magnetic resonance imaging (MRI), fractional anisotropy from diffusion tensor imaging (DTI) and resting-state functional MRI (fMRI). The authors described that CMRglc decrease in the elderly prevailed in the left inferior frontal junction, which was meaningfully connected with macrostructural and microstructural WM turbulences in long association fronto-temporo-occipital fibers but not functional connectivity in the respected region. They concluded that the predominant left inferior frontal junction metabolism decrease in healthy aging is partly accountable for age-related cognitive impairment and is connected with structural disturbance not only in frontal but also in long distant associative WM tract. It is likely that the loss of myelinated fibers reduced synaptic activity in neighboring or projecting cells and/or that diminished CMRglc in WM changes because it changed proximated tract myelinization or because it echoed neuronal bodies degeneration, leading to the degeneration of related axons.

Change of Cerebral Blood Flow

Cerebral blood flow (CBF) has a negative correlation with age. Most studies report that CBF declines in the frontal lobes bilaterally with increasing age [14-17]. The frontal lobes are likely to be influenced disproportionately compared with other regions of the cortex. Probable mechanisms for age-related reductions in CBF include disturbance in controlling mechanisms, reduced function in aging neurons and mild cerebrovascular disease [18].

Martin et al. [19] disclosed reduced CBF in the cingulate, parahippocampus, superior temporal, medial frontal, and posterior parietal gyri in both cortical hemispheres with

increasing age using PET in 30 healthy volunteers aged between 30-85 years. These findings might mirror the cognitive fluctuations that follow aging.

Zhang et al. [16] studied changes of CBF, cerebral blood volume (CBV), cerebral metabolic rate of oxygen (CMRO2), and oxygen extraction fraction (OEF) with age by PET and SPM in 7 young (21.0±1 years) and 7 aged volunteers (60.9±4.7 years). In line with previous reports, this studynot only found that CBF decreased with age, but also detected changes in CBV and CMRO2. Increase in OEF was also detected with advanced age. The increase in OEF with age suggested a greater reduction in CBF than in CMRO2. The most significant decreases of CBF and CMRO2 occurred in the convexity of the frontal cortex and inferior parietal cortex in all of the functional images, while in the WM, the influence of age appeared to be minimal.

Aanerud et al. [17] determined CMRO2 and CBF in 66 healthy volunteers aged between 21- 81 years. It was found that CMRO2 and CBF dropped in large parts of the cerebral cortex, including association areas, but the primary motor and sensory areas were relatively spared. They found significant increaseof OEF in frontal and parietal cortices, excluding primary motor and somatosensory regions, and in the temporal cortex. Because of the inverse relation between OEF and capillary oxygen tension, increased OEF can compromise oxygen delivery to neurons, with possible perturbation of energy turnover. They suggested that the results established a possible mechanism of progression from healthy to unhealthy brain aging, as the regions most affected by age are the areas that are most vulnerable to neurodegeneration.

In line with that, Takada et al. [20], applied PET to quantify CBF and CMRO2 in 32 normal individuals aged between 27-67 yearsCMRO2 in the right and left putamen, left supratemporal, left infrafrontal and left parietal cortices, presented a substantial drop over the course of aging. The age-related decrease in CBF was found to be present only in the left superior temporal cortex. The mean CMRO2 was meaningfully lesser in the elderly (over 51 years old) than in the younger population (under 50 years old), whereas no major difference was detected in mean CBF between the respected groups. The weak correlation of CBF to the age could be partly clarified by the fact that CBF is easily affected by the physiological, psychological and/or environmental elements. The age-related fluctuations of CMRO2 were more noticeable in the association cortices of the left hemisphere than in that of the right hemisphere.

Changes of Neurotransmitter Function

Age-related disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD)are linked with impaired neurotransmission. In neurotransmitter studies, age-related changes of serotonergic, cholinergic and dopaminergic systems associated with mood, memory and motor function are among the most reliably measured functions. There is evidence suggesting that impaired neurotransmission may be responsible for at least some of the behavioral abnormalities of aging. Moreover, age-related neurodegenerative diseases may evolve from the interaction between defects in specific neurochemical mechanisms and yet to be defined pathophysiologic processes [21].

Decline in the functional integrity of the serotonin (5-HT) system related with advancing age have already been described [22-28]. Changes of serotonin system may have role in conditions such as depression and psychosis occuringin late life. A number of studies in age-related serotonin alteration have focused on the serotonin transporter and the 5-HT_{1A} and 5-HT_{2A} receptors [22]. Age-related decline in cortical 5-HT_{1A} (10% per decade) [29] andc 5-HT_{2A} bindings(42±7% and 57±7.2% over an age range of 40 and 58 years), has been reported across studies [22, 30].

The central cholinergic system is believed to contribute to cognitive alterations in aging. However, the precise effects of aging on the cholinergic system are not well understood. Of the studies that have specifically assessed age-related changes in cholinergic receptor binding in the healthy human brain, some have reported a significant decrease in muscarinic acetylcholine receptor (mAChR) binding affinity in the cortex of elderly [31-33], while others have found no change [34], depending on the brain region studied. In vivo human PET or single-photon emission computed tomography (SPECT)studies reported reductions of 8-50% in M_1 and M_2 mAChR binding in cortical and basal ganglia regions, with little change in in the thalamus, hippocampus and cerebellum with increasing age [35, 36]. Conflicting results about neuronal nicotinic acetylcholine receptor (nAChR) binding and expression in humans postmortem brain have also been reported. Unfortunately, in vivo studies of the effects of age on nAChR have been hampered by a lack of suitable radioligands with which the most predominant nAChR subtype in the brain i.e., $\alpha\beta_2$ could be traced [37].

Healthy aging is associated with impairment in motor function resulting from changes in the dopaminergic system. Striatal dopamine levels in the elderly may be only 40% of those in young adults [38]. In vivo imagining of the nigrostriatal dopaminergic pathway via PET or SPECT can be quantified by evaluating dopamine synthesis and storage in the presynaptic terminal with F-18 fluorodopa (FDOPA), or by determining availability of presynaptic dopamine transporter (DAT) or vesicular monoamine transporter 2 ($VMAT_2$) and postsynaptic dopamine receptor by assessing D_1 and D_2 receptors. FDOPA is an analog tracer of levodopa (L-dopa) applied as a biochemical tracer for identifying presynaptic dopaminergic function and the activity of the aromatic amino acid decarboxylase, the enzyme that produces dopamine from its precursor amino acid, L-dopa. Several studies have suggested declining uptake of FDOPA in healthy aging [39-41], however, these results suffer from inconsistency [42, 43]. DAT is a protein positioned at the presynaptic nerve terminal membrane. It plays role in the reuptake of dopamine. Several studies have shown that striatal DAT diminishes with age at a rate of 3.3 to 8.0% per decade [44-50]. Also, dopamine receptors are protein structures placed in neuronal membranes. Five subtypes of dopamine receptors exist in the brain (D1-D5) which can be classified into two groups based on their binding characteristics, namely the D_1-like (D_1 and D_5) and the D_2-like (D_2, D_3 and D_4) families. The availability of D_2-like receptors decreases with age at a rate of 4.0 to 8.4% per decade [50-56] However, studies conducted on D_1-like receptors have yielded inconsistent results.

In addition to motor function, the dopaminergic system also takes part in the cognitive functions. Volkow et al. [57] assessed

the correlation between,neuropsychological test performance and C-11 Raclopride in 31 healthy volunteers, aged between 24-86 years. They found that the age-associated reduction in D_2-like receptor availability of the caudate nucleus was linked to the impairments in both motor function, tested by the Finger Tapping Test, and cognitive performance involving frontal brain regions, including measures of abstraction, mental flexibility (Wisconsin Card Sorting Test), attention and response inhibition (Stroop Color-Word Test, interference score). Backman et al. [58] performed a similar trial in 11 healthy subjects, aged between 21-68 years, with age-sensitive cognitive tests (Dots and trail making A). They showed a gradual age-related worsening in all cognitive tasks and D_2 binding in striatal structures. The results of these studies specify that age-related changes in the striatal D_2-like receptor might partially play a role in age-associated cognitive impairment. DAT's role has also been examined in cognitive function. Mozley et al. [59] measured DAT levels via Tc-99m TRODAT-1 in 66 normal subjects and revealed that women and younger subjects had higher dopamine availability in the caudate nucleus and achieved better results on verbal learning tasks.

Alzheimer's Disease

AD is the most common cause of dementia, accounting for up to 75% of all dementia cases. AD presents itself in different ways, but the most common symptom pattern is a gradual deterioration of the ability to remember new information. This is caused by the disruption of brain cell function in brain regions involved in forming new memories. As damage progresses, individuals experience other difficulties such as memory loss disrupting daily life, challenges in planning or solving problems, difficulty completing familiar tasks, confusion with time or place, trouble understanding visual images and spatial relationships, decreased or poor judgment and changes in mood and personality. Mild cognitive impairment (MCI) refers to the transitional phase between normality and clinically evident dementia. Loss of functional dependence has been used to distinguish MCI from AD as it is defined the feature of AD. MCI is believed by some to be the pre-clinical stage of AD. Longitudinal studies show that a clinical diagnosis of MCI is a significant risk factor for the subsequent development of AD.

FDG Imaging

FDG-PET functions as a non-invasive method for evaluating organ function using regional and global glucose metabolism., FDG-PET measures glucose metabolism, which reflects net brain metabolism, which is an indicator of synaptic activity [60, 61]. Decreased FDG uptake in AD patients indicates impaired synaptic function and correlates significantly with cognitive decline. There is a specific topographic pattern of decreased cerebral glucose uptake, along with a characteristic ensemble of limbic and associated regions that are typically hypometabolic. The anatomy of the AD signature consists of the posterior midline cortices of the parietal (precuneus) and posterior cingulate gyri, the inferior parietal lobule, posterolateral portions of the temporal lobe, as well as the hippocampus and medial temporal cortices. Decreased metabolism in AD gradually worsens throughout the course of the disease. In the early stages, hemispheric asymmetry is common, but as the disease progresses, it usually involves prefrontal association areas, and even primary cortices. The regions that are initially hypometabolic in AD are interconnected and form part of the large-scale distributed brain network known as the default mode network. For MCI patients, less severe hypometabolism is identified. Longitudinal data have shown that FDG hypometabolism parallels cognitive function and continues to decline along with cognitive function.

As AD most commonly occurs in elderly patients influenced by age-related brain atrophy, the precision of PET imaging in this setting is of question. The rather low spatial resolution of PET images produces average signals from the brain tissue and inactive cerebrospinal fluid (CSF) spaces in reconstructed images. Consequently, mean cerebral metabolism as calculated by PET looks lower than the actual rate of metabolism [18]. Lately, the high-resolution anatomical detail obtainable with MRI has led to the development of MR-based approaches to correct PET data for partial volume effect, ensuing in broad applications of PET with structural imaging that further illuminate structural-functional associations.

Amyloid Imaging

For over a century, amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) have been recognized as the neuropathological hallmarks of AD and their presence could only be identified by postmortem examinations using stains and dyes. Consequently, the "amyloid cascade hypothesis" is based on the biochemical changes in Aβ and tau production pathways. The idea is supported by evidence emerged from transgenic mice model of AD that the overproduction or inability to remove Aβ results in Aβ deposition and, subsequently in NFTs precipitation, inflammatory cell death, and cognitive impairment.

A great deal of attention has been paid to a class of PET tracer which targets Aβ peptide as a causative agent in AD. Almost 10 years ago, the first PET study using Aβ peptide tracer i.e., 11C-labeled radiopharmaceutical Pittsburgh Compound B (PiB) was introduced in a living human subject with probable AD. It was constantly claimed that PiB is appropriate for early diagnosis of AD and can be applied for uncovering the pathological alterations commonly seen before clinical cognitive impairment. In 2012, the Food and Drug Administration (FDA) officially permitted the clinical application of Aβ probe Amyvid™ (F18 Florbetapir) for assessment of patients suffering from probable AD. Accordingly, several amyloid probes with claimed specificity for Aβ are currently under investigation at various stages of FDA approval. However, there are a number of warnings about the clinical value of Aβ imaging. Moghbel et al. [62] described several probable problems in this regard, for example partial volume effects causing underestimated SUV data, high ratio of nonspecific to specific WM uptake and discordance between the distribution of Aβ in the brain with histopathological and immunohistochemical studies. Recent critical review of Kepe [63] suggested the lack of in vivo binding validation of these probes and the resulting in misunderstanding of their tissue binding and specificity. Furthermore, the swift peripheral and

central metabolism of these probes and their transportation in the brain are limitations at the core of tracer design and development. Four critical issues are emerging in this regard. First, current Aβ probes do not fulfill the established neuropathological criteria of National Institutes of Aging-Alzheimer's Association for AD diagnosis. Second, diagnostic use of Aβ probe is no longer an intended or plausible indication. Third, the utilization of Aβ probes in monitoring anti-Aβ therapies has been shown to be of really limited use. Last but not least, anti-Aβ therapies have been repeatedly shown to be ineffective. Thus, all of these issues should be resolved before placing Aβ probes on the commercial market.

Parkinson's Disease

PD is manifested by both motor and non-motor symptoms. Motor symptoms are characterized by bradykinesia, resting tremor and rigidity. Pathological hallmark of PD is the continuous damage of pigmented dopaminergic neurons in specifically a brain region called substantia nigra and other brain stem nuclei. This neuronal damage results in a major biochemical deficit in dopamine processing in the striatum, particularly in the putamen. Later in the disease course, the dopaminergic deficit also becomes obvious in other brain regions. The severity of bradykinesia and rigidity in PD has been frequently discovered to be connected with both nigro neuronal loss and striatal dopamine deficiency [64]. Non-motor symptoms in PD include cognitive decline, psychosis, autonomic dysfunction, anosmia and sleep disturbances. Among these symptoms, cognitive impairment has a significant impact on the quality of life in PD patients. PD-associated cognitive impairment could be due to thedopaminergic cell loss in the mesocorticolimbic system, non-dopaminergic neurotransmitter dysfunction (acethylcholine, serotonin, noradrenaline), comorbid AD pathology, cortical and limbic Lewy body pathology and cerebrovascular damage [65]. Cognitive decline is 2-6 times more common in PD patinets than in age-matched healthy subjects and is related to cortical Lewy body disease and, on occasions, simultaneous AD pathology. PET provides the capacity to study dopaminergic system, which may play a role in the diagnosis and understanding the pathophysiology of PD.

FDG-PET

Metabolic changes in patients with PD or other movement disorders are less specific and can overlap with findings in patients with AD [66]. FDG-PET has revealed a typical pattern of decreased resting regional cerebral metabolism at the posterior cingulate, parietal and temporal areas, with slighter damage to the prefrontal cortex in PD patients who become demented [67, 68]. Typically, the primary motor and visual cortices are spared. Temporoparietal cortical hypometabolism can also be detected in a minority of nondemented PD patients, signifying that subclinical cortical Lewy body-induced damage may already be present [69]. Eidelberg et al. [70] and Rougemont et al. [71] reported glucose hypermetabolism in the basal ganglia of early untreated PD patients. Kuhl et al.[72] showed no substantial striatal FDG metabolism in PD patients. Another study revealed reduced glucose metabolism in basal ganglia contralateral to the symptoms in hemiparkinsonismsyndrome [73]. Intriguingly, some studies assessed the metabolic fluctuations across the brain to identify specific brain networks related to bradykinesia and tremor. Eidelberg et al. [74] found that PD-related metabolic covariance pattern (PDRP) associates well with severity of bradykinesia, and manifests as the hypermetabolism of lentiform nucleus,thalamus, lateral frontal cortex, paracentral, inferior parietal and parietooccipital regions. Conversely, parkinsonian tremor appears to be caused by a discrete metabolic network principally damaging the cerebello-thalamo-cortical pathway, or PD tremor-related metabolic pattern (PDTP) [75].

Dopaminergic System Imaging

The function of dopamine terminals in PD patients can be assessed *in vivo* using 3 key methods. The first method is to evaluate the availability of presynaptic DAT, in which several PD studies have revealed substantial drops in its activity [76-79]. Second, FDOPA PET offers a marker of terminal dopa decarboxylase activity and dopamine turnover. Decreased FDOPA uptake in the bilateral posterior putamen with preserved uptake in the head of caudate and ventral striatum were detected in patients with early untreated PD as opposed to the healthy subjects [80-82]. Third, clinical parkinsonism occurs when 40-50% of posterior putamen dopamine function is vanished. The activity is more dropped in the posterior putamen contralateral to the afflicted limbs. Last but not least, VMAT2 availability in dopamine terminal can be scanned using C-11 DTZB, a probe of VMAT2 that shows reduced signal at the caudate and putamen of PD patients [83]. The association between striatal dopaminergic fluctuations and the severity of motor dysfunction is well recognized. A noteworthy converse association has been established between Hoehn and Yahr score and FDOPA uptake in both putamen and caudate nuclei [84]. FDOPA uptake in the putamen also associates well with total UPDRS motor score and specific clinical characteristics of bradykinesia and rigidity [85]. Moreover, a major negative connection between total unified PD rating scale (UPDRS) motor score and DAT ligand uptake in the caudate nucleus and putamen has been proven [86].

While the pathophysiologic cause of PD is thought to be presynaptic dopaminergic dysfunction, radioligands of postsynaptic dopaminergic neuron can be also applied to evaluate nigrostriatal signal alterations. Rinne et al. [87] and Sawle et al. [82] used C-11 Raclopride to examine D_2 receptor in PD patients and showed escalated C-11 Raclopride activity (up-regulation) in the striatum contralateral to hemiparkinsonian symptoms in early disease. As the disease advanced, down-regulation of D_2 receptor was found to be th case [88].

Deterioratin of cognitive function in PD has been investigated in the context of the dopaminergic system. A significant positive link between decreased FDOPA uptake in the caudate nucleus and poor performance on tests of visual memory and immediate and delayed verbal memory has been established by Jokinen [89]. Cropley et al. [90] discovered that reductions in putaminal FDOPA uptake can forecast performance on Wisconsin Card Sorting Test in nondemented PD patients. Others verified a correlation between the density of DAT at the caudate

and putamen nuclei and cognitive dysfunction, as measured by object alternation and conditional associative learning [91] and Wisconsin Card Sorting and digit ordering [92].

Other Neurotransmitter Tracers

C-11 WAY 100635, a PET ligand for the serotonin 5-HT_{1A} receptor, has been applied to evaluate the pathogenesis of motor symptoms in PD, where a 27% reduction in tracer binding in the midbrain raphe was discerned as compared to normal volunteers. This likely echoes decreased 5-HT_{1A} receptor availability. The reduction of C-11 WAY 100635 binding associated well with the composite tremor score [93].

Politis et al. [94] used C-11 DASB PET, a marker of serotonin transporter availability, in 30 PD patients and 10 age-matched volunteers. They found a significant binding reduction in striatal, brainstem, and cortical regions in PD patients, however, no correlation was found with UPSRS score, Hoehn & Yahr staging, disease duration and level of exposure to dopaminergic therapy. The same investigators [95] performed further studies with the same tracer and found a correlation between serotonin transporter dysfunction and depressive symptoms in PD patients.

Bohnen et al. [96] performed a cross-sectional study in 44 nondemented PD patients and 15 controls using PET with acethylcholine analogue C-11 PMP to assess acethylcholinesterase (AChE) activity and C-11 DTBZ to determine nigrostriatal dopaminergic function. They revealed that although nigrostriatal dopaminergic activity was comparable between fallers and non-fallers, the fallers had meaningfully poorer thalamic AChE activity that both controls and non-fallers. Thalamic cholinergic dysfunction probably echoes loss of function of the pedunculopontine nucleus, which is the primary cholinergic innervator of the thalamus. Therefore, these outcomes propose a connotation between cholinergic alteration and a propensity to fall in PD patients. Cholinergic degeneration also disclosed a significant relationship with cognitive deterioration in PD patients. The acethylcholine analogue binding in the cerebral cortex was shown to be additionally decreased in PD with dementia (PDD) than nondemented PD patients, and associated well with performance on tests of working memory, attention and executive functions [97].

Novel Quantitative Approaches and Application in Neurodegenerative Diseases

In the 1980s, CT and low-resolution PET instruments were used to study patients with AD and other central nervous system (CNS) disorders [98]. Afterwards, the high resolution detail achieved by MRI eventually led to the development of MR-based techniques which were able to correct PET data for partial volume effects. The key segmentation task in MR-guided PVC is the extraction of cerebral tissue classes, i.e. GM, WM and CSF. Several studies have applied MR-derivedtotal brain CSF volume to adjust whole brain metabolic rate for age and disease-associated cerebral atrophy. Kohn et al. [99] explained a novel computerized system established to process standard spin-echo MRI data to assess GM, WM and CSF volumes. In phantom experiments, the estimated volumes corresponded closely to the true volumes (r=0998), with a mean error < 1 cm^3 (for phantom volumes ranging from 5-35 cm^3). Excellent intra- and inter-observer reliability were also noted. In a clinical validation study with actual brain images of 10 human subjects, the average coefficient of variation among observer for the measurement of absolute brain and CSF volumes was 1.2% and 6.4%, respectively. The intraclass correlation for three expert operators was found to be greater than 0.99 in the measurement of brain and ventricular volumes, and greater than 0.94 for total CSF volume. Kohn concluded that this technique for analyzing brain MRI images demonstrated acceptable level of accuracy, and could be applied to determine brain and CSF volumes for clinical purposes. This methods could be of assistance in making a correlation between neuroanatomic evaluations with behavioral and physiological parameters in neuropsychiatric disorders.

Tanna et al. [100] implemented this computerized segmentation method in an analysis of digitized T2-weighted MRI of 16 normal elderlies and 16 AD patients. They calculated ventricular and extraventricular CSF and evaluated the impacts of aging and AD on brain function using FDG-PET. In both groups, the severity of atrophy acquired by these methods was used to correct PET-derived metabolic rate. The results revealed that patients with AD had greater total extraventricular, total ventricular and third ventricular CSF volumes and less brain volumes than those of the control participants. Patients with AD showed a more noticeable decrease in the brain volumes and a greater escalation of CSF volumes with advancing age than the control group. Also, by applying the partial volume correction factors we found thatAD patients had a 25% escalation in corrected whole-brain metabolic rates compared with the control group, who had only a 15.8% rise. The authors determined that the application of this technique could offer a basis for further studies of aging and dementia by measuring the precise rate of local metabolism in these settings.

Labbe et al. [101] used 3D MRI-based3D correction of human PET data. They measured atrophy and metabolism in 12 AD patients and controls by both T1-weighted MRI and high and medium resolution PET scan. They found that global cortical metabolism increased after PVC by around29% and 24% for tomographs acquired with medium and high resolution PET scanner, respectively, whereas cortical metabolism increased by 75% and 65% for the respective tomographs in AD patients.

In a study conducted on 139 healthy subjects, aged between 24-81 years, Yanase et al. [102] could efficiently correct partial volume effect (PVE) in measuring cerebral glucose metabolism with advancing age, using segmented GM volume from coregistered MRI. The lower mean metabolic rates detected before correction for PVE could be justified by age-related atrophy in the medial frontal and bilateral perisylvian gyri.

Berkouk et al. [103] assessed the contribution of GM volume and GM activity of 18 health subjects. They applied average GM and WM PVE-corrected FDG uptake values onto coregistered and segmented MRI data sets to generate a virtual PET in which the activity was proportional to GM volume and resolution emulated the PET system. Comparison between the raw PET and virtual PET were performed across the sample of subjects. It was revealed that the expected contribution of functional

activity was independent of local differences in GM volume and disclosed marked heterogeneities in functional activity per unit of GM volume in various structures. There was significant hyperactivity in most GM structures of the dorsal brain except the thalamus, along with significant hypoactivity of temporal lobe, hippocampus and cerebellum. These findings suggested that this method could be utilized in investigations of pathological states.

Samuraki et al. [104] investigated the effect of PVE correction by a MR-based algorithm on brain FDG-PET results in 39 patients with mild AD and 73 controls, and compared the results of PVC with those obtained by morphological analysis of GM volume concentration using VBM. Reduced FDG uptake in the posterior cingulate gyri and parietotemporal lobes was found in AD patients in both corrected and uncorrected PVE images, supporting the notion that decreased FDG uptake in these areas is not the result of cortical atrophy. Intriguingly, PVE correction revealed relatively preserved FDG uptake in hippocampal areas, despite the GM loss in medial temporal lobes that was revealed by VMB. This suggests that compensatory mechanisms may play a role in patients with mild AD. The authors concluded that PVE correction combined with morphological approaches using MRI and VBM is of value for better understanding early AD.

Bural et al. [105] assessed a quantitative MRI segmentation scheme that allowed for definite SUV measurement of the local GM, WM, and CSF volumes in 5 subjects with normal MRI and FDG-PET scans. This approach overcame the troubles accompanying conventional low resolution imaging methods for determining the actual metabolic activity of GM. The authors measured the volumes of GM, WM and CSF via a distinct segmentation method on MRI, followed by computation of the mean SUV demonstrating the whole brain metabolic activity from FDG-PET images. They also calculated the WM SUV from the upper tranaxial slices of the centrum semiovale on FDG-PET. GM, WM and CSF volumes were summated to determine whole brain volume and global cerebral metabolic activity by multiplying the mean SUV by total brain volume. The whole-brain WM metabolic activity was determined by multiplying the mean WM SUV by its volume. CSF metabolic activity was considered to be zero. Thus, by subtracting the global WM metabolic activity from that of the whole brain, they calculated the total GM metabolic activity alone. Accordingly, by dividing global metabolic activity of GM by its volume, a precise SUV for GM alone was achieved. This study found that the brain volumes ranged between 1100 to 1546 cm^3. The mean SUV for the total brain was between 4.8 to 7. Also, global cerebral metabolic activity was found to be between 5565 to 9566 SUV cm^3. Additionally, the mean SUV for WM was revealed to be between 2.8 to 4.1. On the basis of these measurements, they reported that the GM SUV in the sample examined alternated between 8.7 and 11.3.

Curiati et al. [106] used MRI for the correction of PVE in FDG-PET images of 55 cognitively healthy elderly participants. The correlation between age and regional cerebral metabolism was assessed using SPM5 with and without PVC. They found two large clusters of age-related metabolic decreases in the overall sample in the left orbitofrontal cortex and the right temoporolimbic region, encompassing the hippocampus, the parahippocampal gyrus and the amygdala. However, the correlation was not shown to be significant in PVC images. The finding suggested that age-related functional brain variability in cognitively healthy elderly individuals is largely secondary to the degree of regional brain atrophy, and appropriate PVC is a key tool in neuroimaging investigation.

Coello et al. [107] studied the correction of PVE in subcortical WM regions by using synthetic FDG-PET volumes derived from segmented MR volumes. The method consisted of solving the convolution problem at a voxel level by Local Regression Analysis (LoReAn) using regional information from coregistered MR volume. This method was presented and validated using the region-based geometric transfer matrix (GTM) algorithm with synthetic and clinical data.

Hu et al. [69] used MRI segmentation for PVC by SPM96 in 10 nondemented PD patients and 9 age-matched controls who underwent FDG-PET imaging for investigation of cortical function. FDG-PET revealed absolute bilateral reduction in glucose metabolism after PVC in the posterior parietal and temporal GM in nondemented PD group.

The accuracy of PVC algorithm is highly dependent on the degree of precision achieved by MRI-PET realignment and MRI segmentation procedures. The following studies compared the performance of commonly used brain MR segmentation algorithms using simulated phantoms and clinical data acquired from realistic conditions.

Quarantelli et al. [108] compared 4 distinct PVC methods in terms precision by running the software over a large range of segmentation, coregistration and resolution to estimate error. The approaches included those that were proposed by Meltzer (M-PVC) [109], Muller-Gartner (MG-PVC) [110] and Rousset (R-PVC and modified Muller-Gartner or mMG-PVC) [111, 112]. They found the greatest accuracy in the ROI-based R-PVC approach. When voxel-based PVC images were desired, the mMG-PVC appeared to be the most appropriate.

A comparative evaluation of three brain MR algorithms including SPM2, Expectation Maximization Segmentation (EMS) and Histogram-based Segmentation algorithm (HBSA) in simulated phantom and clinical data was achieved by Zaidi et al.[113]. The segmented tissues of patients' brain MRIs were given as input to the ROI-based GTM algorithm, and quantitative comparisons were made. The results of digital MRI phantom studies suggested that the use of HBSA produced the best performance for WM classification, while EMS is advantageous for GM classification. However, segmentation performed on clinical data by three algorithms, especially when lesions were present, showed greatly similar outcomes and thus might be used interchangeably. The authors concluded that the corrected activities of PVE in some regions of the brain show large relative differences when performing paired analysis on two algorithms, indicating that the segmentation method for ROI-based PVC must be chosen judiciously.

Gutierrez et al. [114] compared four brain MR segmentation algorithms bundled in the releases of SPM package, including SPM99, SPM2, SPM5 and SPM8, that were aoolied to segment clinical T1-weighted MR brain images. The resulting partitions were used as an input for the 2 compartment voxel-based PVC

algorithm. Subsequently, the impact of these algorithms on PVC in clinical FDG-PET brain imaging was assessed. The authors found that, as compared with SPM5, the previous releases of SPM (SPM99 and SPM2), result in larger GM regions (~20%) and smaller WM regions (between -17% and -6%), which created a non-negligible bias in PVC PET activity estimates (between 30% and 90%). In contrast, the more recent release (SPM8) results in similar performance with SPM5. They concluded that the consolidated Bayesian formulation in SPM5 and SPM8 versions was the most relevant improvement into SPM segmentation procedure.

Recently, the feasibility of using an adaptive contrast-oriented thresholding algorithm with local background partial volume correction algorithm software for quantitative PET analysis has been demonstrated [115-117]. This technique utilizes a novel adaptive thresholding and background subtraction algorithm to identify lesion volume within a general user-defined area (mask) [118]. It then applies PVC and provides quantitative measurements including volume, SUVmax, SUVmean and metabolic volumetric product or metabolic volumetric product (MVP) (mean SUV*volume). All data are provided in an automated, non-biased manner, without MRI coregistration, and image convolution or ROI delineation. Additionally, this software requires minimal experience and can be applied to any image in minutes [117].

Global Metabolic Activity Assessment and Application in Neurodegenerative Disease

Image segmentation and global disease assessment enhance the accuracy of measurements made by FDG-PET imaging [119, 120]. Total lesion glycolysis and whole body metabolic burden have also been used in the literature to describe this approach [119-125]. Global metabolic activity is grounded on multiplying average PVC SUV to the volume of the organ of interest acquired from anatomical modalities such as CT or MRI. The multiplicative product is termed MVP, as presented in the equation below:

MVP=PVE corrected mean SUV× Metabolic active volume

The idea was first presented by Alavi et al. [126] in the evaluation of the brain in AD patients and age-matched healthy subjects. By multiplying segmented brain volumes from MRI by mean cerebral metabolic rates for glucose, substantial differences between two groups could be verified. This method, however, necessitates computing tissue volume by employing modern computer-based algorithms and PVC measurements of metabolic activities at each ROI. The global metabolic activity evaluation of disease is beneficial in neuropsychiatric disorders, where the calculation of glucose metabolism in total brain tissue can be a more trustworthy metric of the state of disease than that of a single region [127-130].

Another study by Alavi et al. [120] examined 20 probable AD patients and 17 age-matched controls who underwent FDG-PET and MRI. They measured atrophy-corrected average CMRglc by the following equation:

$$\text{Atrophy} - \text{corrected average CMRglc} = \frac{\text{Mean CMRglc}}{\text{\% brain tissue in the intracranial volume}}$$

Atrophy-corrected average metabolic rates were found to be 3.91±1.02 and 4.43±0.87 (mg of glucose per 100 cm^3 brain tissue per minute) for AD and controls, respectively, with no substantial intergroup difference. However, atrophy-weighted whole brain metabolism (measured by multiplying the brain volume by the average metabolic rate) exhibited a significant difference between the two groups (29.96±7.9 for AD and 39.1±7.0 for controls, $p<0.001$). Absolute whole brain metabolism (determined by multiplying atrophy-corrected average CMRglc by brain volume) also showed a major difference: 37.24±9.65 in AD and 45.09±8.52 in controls, $p<0.014$). These measurements associated well with mini-mental status exam (MMSE) score. These data confirmed that although the metabolic rate per unit weight of the brain is unaffected in AD patients, atrophy-weighted total brain metabolism and absolute whole brain metabolism are considerably influenced. The authors concluded that both indices could be sensitive correlates for cognitive impairment in AD.

Musiek et al. [117] assessed brain volume and FDG metabolism in 14 AD patients and 18 age-matched controls and compared the results with volumetric MRI data. They found that whole brain volume when measured by this method and MRI and whole brain MVP were meaningfully lower in AD patients and precisely distinguished them from controls. Global MVP derived by this approach was 21.1% lower in AD patients than controls ($p<0.01$) and cerebral cortex MVP showed a larger difference between groups (31.6% decrease in AD, $p<0.01$).

Conclusion

Advanced functional studies in brain imaging with novel quantitative assessment have recently gained a great deal of attention. These techniques allow investigators to understand normal aging and pathophysiologic changes of neurodegenerative diseases and may subsequently be of great value in therapeutic strategies development. MRI techniques have been developed for the correction of PVE in PET imaging and the improvement for PET quantification. The new technique of adaptive thresholding and background subtraction in novel software also holds promise in this regard. In the coming years, this approach may play a role in PVC and quantification, limiting the need of high-resolution segmented images.

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